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Selectivity in IgG Subclass Response to Live Plague Vaccine in Humans

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Abstract

Attenuated *Yersinia pestis* strain EV NIIEG is a licensed live plague vaccine (LPV) for human use in Russia that can elicit protection against both the bubonic and pneumonic forms of disease. However, little is known about the mechanisms underlying the formation of immunity to *Y. pestis* provided by this vaccine. Our recent study reported a prevalence of specific IgG antibodies to the capsular antigen F1 and the type three secretion system (T3SS) structural subunit YscF in humans immunized with live plague vaccine. In this study, IgG subclasses of antibodies to the plague antigens F1 and YscF in the sera of vaccinees were determined by using an enzyme-linked immunosorbent assay (ELISA) with monoclonal antibodies. IgG subclass antibodies to F1 antigen were predominantly IgG1, although IgG2 and IgG4 subclasses were detectable. The IgG1 titers were markedly higher in donors who received multiple annual injections, while the IgG2 and IgG4 titers showed no increase and stayed low in all donors. The IgG1 anti-F1 remained detectable even 20 years post-vaccination, suggesting a long-term immunity. Sera of YscF-positive donors also contained predominantly IgG1-specific antibodies. The IgG2 and IgG4 titers to YscF were undetectable in all donors, including those who received multiple vaccinations. In conclusion, we describe for the first time that IgG1 is a dominating isotype for both F1 and YscF antigens in humans immunized with live plague vaccine.

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Keywords: Yersinia pestis, live plague vaccine, vaccine strain EV NIIEG, human protective immune response;

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1. Introduction

Yersinia pestis strain EV NIIEG has been used for decades in Russia and other countries of the Former Soviet Union as a human prophylaxis against plague. This vaccine can provide protection against both major forms of the disease, such as bubonic and pneumonic plague [1-11]. Specific IgG antibodies to the capsular antigen F1 have been considered to be a valuable marker of immunity to *Y. pestis*, although a duration of the existence of these antibodies in humans vaccinated with EV NIIEG remains unclear [12, 13]. Moreover, a subclass-specificity of these antibodies has been never investigated. Recently, we reported that antibody to YscF, a structural subunit of the T3SS apparatus, could be detected in humans immunized with live plague vaccine [14]. The current study was undertaken to address questions both on the duration of an antibody response and subclass specificity for the F1 and YscF antigens.

2. Materials and methods

The titers of specific antibody (Ab) isotypes IgG1, IgG2, IgG3, IgG4, IgM and IgA to either *Y. pestis* F1 or YscF were evaluated by using an ELISA with a panel of subclass- specific monoclonal antibodies (MAbs). Briefly, microtiter plates of Immulon 2 HB (Thermo Scientific) were coated with 0.2 μg of highly purified recombinant *Y. pestis* F1 or YscF antigens, obtained after cloning, and production of these proteins in *E. coli* in the form of fusion peptides with His-Tag, followed by their purification by Ni^{2+}- chromatography [8]. Two-fold serial dilutions of sera obtained from donors who received multiple annual immunizations with the live plague vaccine EV NIIEG were added to the plate, which was then incubated at room temperature (RT) for 2 hours. Subclass-specific murine MAbs (Rosmedbio, St. Petersburg, Russia) were added at concentrations of 12.5-50 μg/ml, and microplates were incubated for 2 h at RT. Goat anti-mouse IgG (H & L) labeled with HRP (Chemicon International) was used as the secondary Ab. TMB (Sigma) was the chromogenic substrate.

3. Results

Antigen-specific IgG subclasses, such as IgG1, IgG2, and IgG4, were found in the sera of F1-positive donors (n = 5) who received a different number of immunizations with the EV NIIEG vaccine. The IgG1 titers varied between these individuals and generally were increased in those vaccinees who received several annual immunizations (Fig. 1a). The IgG2 and IgG4 titers showed no increase regardless of the number of vaccinations, and stayed low in all donors. The IgG1 was a dominant subclass of Ab to YscF, although there was no tendency toward an increasing IgG1 titer with the number of vaccinations (Fig. 1b). The IgG2 and IgG4 subclasses were not detected in either YscF- reactive donor serum (n = 4).

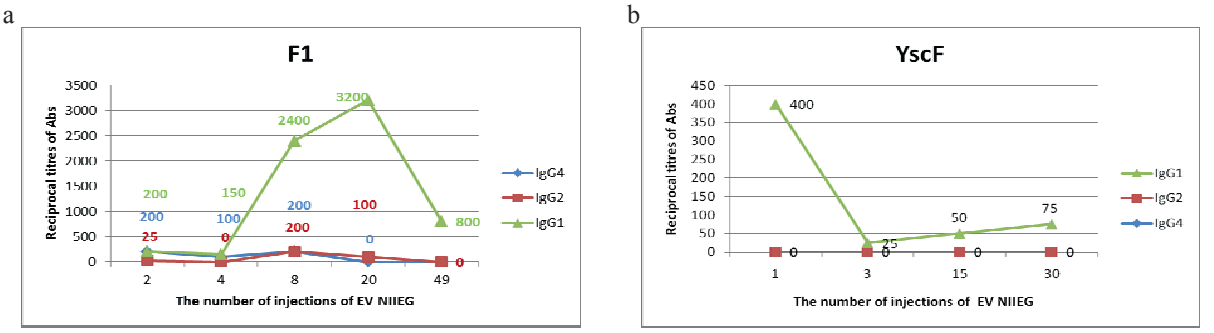

Fig. 1. Titers for IgG subclasses in serum of individual donors who received multiple annual administrations of LPV. (a) anti – F1 antibodies; (b) anti – YscF antibodies..

Once they appeared, however, anti-F1 IgG1 antibodies circulated in vaccinated individuals for up to 20 years (observation period) after the last administration of LPV. In contrast, IgG2 and IgG4 were hardly detectable after a short post-vaccination period (Fig. 2a).

Similarly, only IgG1, but not IgG2 and IgG4, were found in YscF-positive donors at low levels during the first several years after the last immunization with EV NIIEG (Fig.2b).

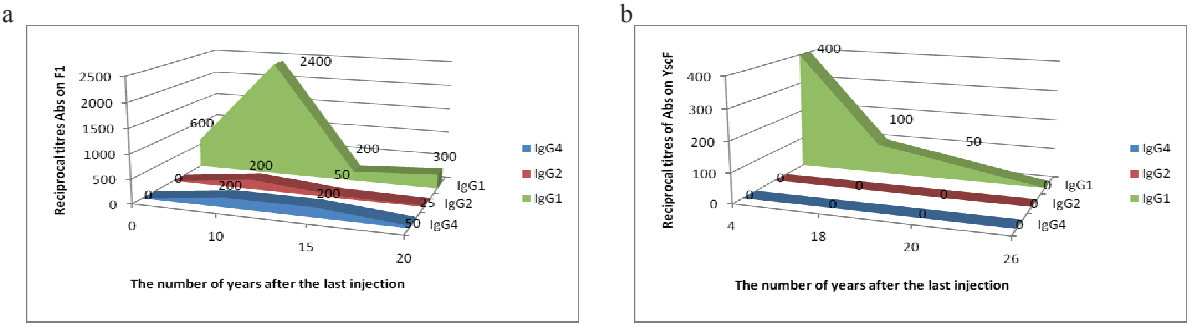

Fig. 2. Titers for IgG subclasses in serum of donors versus the number of years since the last immunization. (a) anti-F1 antibodies; (b) anti-YscF antibodies.

Importantly, a high level of anti-YscF antibody of IgA subclass was detected in the sera from two vaccinees who received either three or fifteen inoculations of EV NIIEG (Fig. 3a). These IgA antibodies remained detectable for a long period of time after the last immunization (Fig. 3b). No significant dynamics in anti-YscF antibody of the IgM subclass was observed in these experiments (Fig.3).

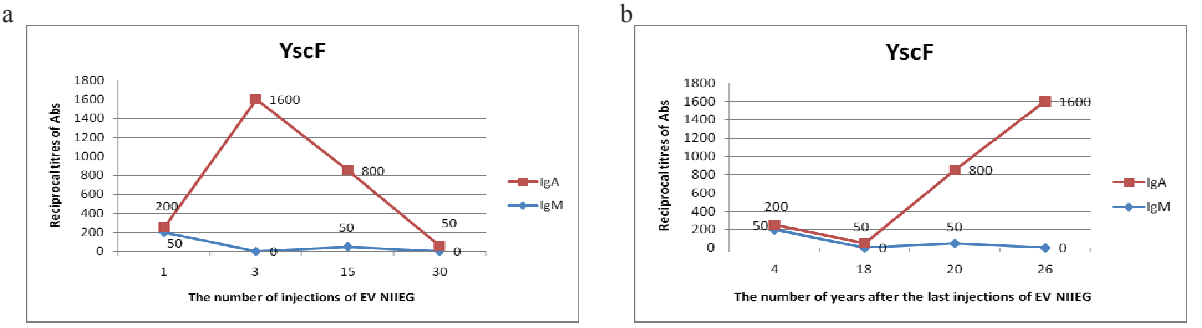

Fig. 3. Titers for YscF-specific IgM and IgA antibodies in sera of donors versus either a number of annual administrations of LPV (a), or a number of years post last immunization (b).

4. Conclusions

1. Isotype IgG1 is a domination subclass of IgG for F1 and YscF antigens in humans immunized with live plague vaccine.
2. IgG1 to YscF can serve as an early indicator of response to LPV, while IgG1 to F1 can account for a marker of long-lasting immune response in vaccinees with multiple immunizations.
3. A strong IgA response to YscF can be considered as an additional marker for detection of a long-lasting humoral immune response to LPV in humans.

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